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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/645,451

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Joseph L. Bryant

4115-150 CIP DIV

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW

PO BOX 14329

RESEARCH TRIANGLE PARK, NC 27709

EXAMINER

NOBLE, MARCIA STEPHENS

ART UNIT

PAPER NUMBER

1632

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/645,451	<b>Applicant(s)</b> BRYANT ET AL.	
	<b>Examiner</b> MARCIA S. NOBLE	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3,4 and 6-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,4 and 6-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/8/2009</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Claims***

Claims 1, 3, 4, and 6-10 are pending. Claim 1 is amended by Applicant's amendment, filed 4/30/2009. Claims 1, 3, 4, and 6-10 are under consideration.

### ***Withdrawn Rejections***

The rejection of claims 1, 3, 4, and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Browning et al (PNAS 94:14637-14641, 1997; of record), in further view of Bennett (US 5,625,125 patent date:4/29/1997), as set forth in the Office Action, mailed 1/30/2009 (pp. 4-7).

The following new rejections are necessitated by the amendment to the claims:

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is “undue”.

The amended claims are drawn to a transgenic rat, whose genome comprises a transgene encoding a CD4 protein sufficient for binding to gp120 operably linked to a PBMC-specific promoter, wherein CD4 is expressed on PBMC of the transgenic rat and wherein the expressed CD4 is capable of binding gp120, and wherein the rat develops active HIV infection after exposure to HIV, with expression of antibodies or viral antigen in sera thereof.

The specification teaches the production of a transgenic rat comprising a transgene encoding human CD4 gene operably linked to a lymphocyte specific protein tyrosine kinase p56 lck promoter (Example 22, p. 50, lines 1-16). These rats were born with bilateral small commissures and the rats were smaller in size than their non-transgenic littermates. The specification further teaches that other than these disclosed phenotypes, the transgenic rats were phenotypically identical to non transgenic rats (p.

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50, lines 17-19). This is the only reported phenotype for the disclosed transgenic rat by the specification. The specification discloses, "Such animals are expected to be able to become infected by HIV, since it has been shown that a rat fibroblast line expressing hCD4 is infectable with HIV-1...Therefore, active HIV-1 infection of a huCD4 transgenic rat or T cells thereof should be possible." (See p. 20, lines 18-22). Thus, the specification contemplates that the transgenic rat of the claims should develop the phenotype of active HIV-1 infection. The specification further contemplates methods of using the transgenic rats to determine HIV infection after exposure to HIV, antibody detection, and detection of viral antigen in sera (p. 51, lines 3-22). However, the specification fails to demonstrate that the claimed transgenic rats develop active HIV infection, express antibodies, and viral antigen in sera as claimed. There is no guidance or evidence of record that shows that the transgenic rats of the instant invention develop active HIV infection after exposure to HIV, with expression of antibodies or viral antigen in sera thereof.

Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). Mullins et al states that not all animals express a transgene

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sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed on a case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall. Theriogenology 45:61, par 2, line 9 to p. 62, line 3, 1996.) Mullins et al disclose that "the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to the another." (Mullins et al. J Clin Invest 98:S39 summary, 1996) Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron Mol Biotech 7:256, col 1-2, bridging par, 1997). Factors influencing low expression, or lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron Mol Biotech 7:256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron Mol Biotech 7:256, lines 10-13). Furthermore, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal sites, and that the position of the transgene effects

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expression, and thus the observed phenotype (Sigmund Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000).

While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. As discussed above, the art teaches that multiple factors, in particular position effect and random insertion of the transgene, hinder the predictability of a contemplated phenotype, as in the case of the claimed transgenic rat. In other words, the art teaches an artisan would not have a predictable degree of successfully in obtaining a claims CD4 transgenic rat with the phenotype of active HIV infection, expression of antibodies and viral antigen in the serum as contemplated because the art suggests multiple factors such as position and integration of the transgene results in variable expression of the transgene and thus variable phenotypes. Since the specification only contemplates a CD4 transgenic rat with a specific phenotype of active HIV infection, expression of antibodies, and viral antigen in serum and fails to provide specific guidance to overcome the unpredictabilities in the art, the specification fails to provide an enabling disclosure of a CD4 transgenic rat with the contemplated phenotype of a active HIV infection, expression of antibodies, and viral antigen in serum as claimed.

Therefore at the time of filing the skilled artisan would need to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, and 6-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "active HIV infection". This recitation is indefinite because the properties encompassed by "active HIV infection" are not apparent. Claims 3, 4, and 6-10 depend upon claim 1.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner, Art Unit 1632